REMARKS/ARGUMENTS

Claims 1-3 and 10-12 stand rejected under 35 U.S.C 102(b) as being aniticipated by Amersham Plc, WO2001/096895. Further, claims 4-9 and 13-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amersham Plc. in view of Streetman, D.S. et al. The application has been amended. The claims have been amended. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

The Applicant has carried out the following amendments to the claims:

Claim 1 has been amended such that:

- the method is for selecting volunteer patients for a clinical trial by phenotyping a group of individuals,
- the method includes determining in vivo CYP 450 activity,
- steps c-e) are included for comparing characteristics, grouping individuals with similar characteristics and selecting a group of volunteer patients showing a specific phenotype for use in a clinical trial.

Claim 1 has been combined with former claims 5-8. Further, basis for the amendments is found on page 1, lines 28-31, page 15, lines 22-27 (phenotyping of a clinical trial group), page 4, lines 4-5 and former claim 14 (CYP 450 activity) and page 15, lines 22–27 (grouping and selecting).

Claims 2-8 and 13-14 have been cancelled.

Claim rejections – 35 USC § 102

Claims 1-3 and 10-12 stand rejected under 35 U.S.C 102(b) as being aniticipated by Amersham Plc, WO2001/096895. This rejection is respectfully traversed.

Claim 1 as now amended relates to a **method for selecting volunteer patients for a clinical trial by phenotyping of a group of several human individuals** by determining *in vivo* CYP 450 activity wherein

- NMR active nuclei in samples that are collected from said individuals who were preadministered with more than one probe compounds which are substrates, inducers or inhibitors of CYP450 are hyperpolarised
- the hyperpolarised samples are analyzed by NMR spectroscopy and thereby the characteristics of said several human individuals are determined
- the characteristics of said several human individuals are compared
- individuals who exhibit the same or similar characteristics are grouped into groups of volunteer patients showing a specific phenotype, and
- selecting a group of volunteer patients showing a specific phenotype and using it in a clinical trial.

Due to the use of volunteer patients with different biological characteristics and behaviours in clinical trials, the performance of a drug in a clinical trial may exhibit great variation, i.e. from showing no effect at all to undesired toxicity or other adverse effects (see page 1, line 10 to page 2, line 12). Hence there is a need to identify and use volunteer patients with similar biological characteristics and behaviours, i.e. a specific phenotype, in clinical trials. The present invention provides with the method of claim 1 a method to identify volunteer patients with a specific phenotype and selecting a group of volunteer patients having a specific phenotype for use in a clinical trial.

WO2001/096895 discloses in a third aspect **a method for investigating the state of a biological system** (page 13). In one embodiment, the method is used for investigating the

state of two or more biological systems to determine whether they are in the same or in different states (page 5, lines 2-3).

The above-mentioned prior art method comprises steps wherein
- NMR active nuclei in samples that are collected from said biological systems which were subjected to a test compound (page 14 line 16) are hyperpolarised (page 13, lines8-12)
- the hyperpolarised samples are analyzed by NMR spectroscopy and thereby the NMR pattern of said biological systems are determined (page 13, line 15)
- the patterns of the biological systems which reflects the state said system is in are compared to determine whether they are in the same or in different states (page 13, line 17 in combination with page 5, lines 2-3).

In the following the Applicant provides a table to describing the method of claim 1 and the method disclosed in WO2001/096895 for easier comparison:

Claim 1	**WO2001/096895**
method for selecting volunteer patients for a clinical trial by phenotyping of a group of several human individuals by determining in vivo CPY 450 activity wherein	method for investigating the state of several biological systems wherein
NMR active nuclei in samples that are collected from said individuals who were preadministered with more than one probe compound containing at least one NMR active nuclei, wherein the probe compounds are substrates, inducers or inhibitors of CYP450 are hyperpolarised	NMR active nuclei in samples that are collected from said biological systems which were subjected to a test compound are hyperpolarised

the hyperpolarised samples are analyzed by NMR spectroscopy and thereby the characteristics of said several human individuals are determined	the hyperpolarised samples are analyzed by NMR spectroscopy and thereby the NMR pattern of said biological systems are determined
the characteristics of said several human individuals [which reflect their specific phenotype] are compared	the patterns of the biological systems [which reflects the state said system is in] are compared
individuals who exhibit the same or similar characteristics are grouped into groups of volunteer patients showing a specific phenotype	it is determined whether the biological systems are in the same or in different states
a group of volunteer patients showing a specific phenotype is selected and used in a clinical trial	

From the table above it is apparent that there are differences (as underlined) between the method of claim 1 and the method disclosed in WO2001/096895. Thus WO2001/096895 fails to disclose each and every element of claim 1. As WO2001/096895 fails to disclose each and every element of the claimed invention, Applicants respectfully submit that claim 1 is novel thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections - 35 U.S.C 103

Claims 4-9 and 13-16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Amersham Plc. in view of Streetman, D.S. et al. This rejection is respectfully traversed.

The Applicant has shown that are differences between the method of claim 1 and the method disclosed in WO2001/096895. The methods are intended for different use.

WO2001/096895 discloses the following uses:

- Quality assurance testing of systems that are intended to be the same, e.g. cell cultures (page 14, last paragraph)
- Investigating responses of a biological system to a compound about which relatively little is known (page 16, 1st paragraph)
- Studying plants (page 16, 2nd paragraph)

Clearly, these uses do not point in the direction of selecting volunteer patients with a specific phenotype and using said volunteer patients in a clinical trial. Thus the teaching of WO2001/096895 would not have prompted the skilled person faced with the objective of providing a method to identify and select volunteer patients with a specific phenotype to modify or adapt the method of WO2001/096895 for such a purpose.

Additionally, Streetman, D.S., et al discloses an evaluation of urinary midazolam MR as an index of hepatic CYP3A activity. For phenotyping blood/urin samples were LC/MS/MS analysed. Hence, Streetman is directed to methods of phenotyping, but for another purpose and by other method steps than provided by the claimed invention. The claimed method includes a fast and simple method for phenotyping of human individuals, analysing samples from human individuals preadministered with compounds containing NMR active nuclei by NMR spectroscopy. Streetman provides a method wherein samples are subjected to solid phase extraction prior to analysis by liquid chromatography and mass spectroscopy. A disadvantage of this method is that work-up of samples is time consuming. Moreover, due to reduced recovery of the probe drugs and their metabolites after solid phase extraction it might be difficult to detect small amounts of metabolites. There is hence no teaching or suggestion by Streetman to use a fast and simple NMR spectroscopy method, which also is a very different method from LC/MS/MS, in phenotyping.

As neither WO2001/096895 nor Streetman, either alone or in combination, disclose, teach, or suggest the instant invention, Applicants respectfully submit that present invention is

patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1, 9-12, and 15-16, is in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to the Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,

_/Robert F. Chisholm/____
Robert F. Chisholm
Reg. No. 39,939

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6905